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Exploration of the structural differences between safe and unsafe NSAIDs using 3D molecular similarity

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Introduction: The potential benefit of non-steroidal anti-inflammatory drugs (NSAIDs) is restricted by their adverse drug reaction (ADR) profiles. Evidence is showing the cardiovascular ADRs to be most likely an off-target effect. The aim of this study is to identify 3D shape and feature similarities between "safe" and "unsafe" NSAIDs, with safe defined as NSAIDs in frequent or first line use (such as naproxen) and unsafe defined as withdrawn drugs or those with poor profiles.

Method: A systematic review of the literature was conducted in order to identify experimental, marketed and withdrawn NSAIDs. SMILES strings were obtained from PubChem and used to generate initial 3D conformers. Schrodinger LigPrep was used to generate lowest energy conformers with protonation state adjusted to pH 7.4 (+/- 1.0). Full matrix of 3D similarity coefficients was calculated using shape and feature similarity (SHAFTS). DS Visualizer was used to visually inspect the overlay of 3D structures and identify differences in the similar structures. Detailed analyses were made between a "safe" NSAID, naproxen, and "non-safe" rofecoxib.

Results: Naproxen and pirprofen have a SHAFTS similarity coefficient of 1.56 with similar scaffold (Figure 1A). Visual inspection revealed pirprofen contains an aromatic ring out of plane with the naproxen scaffold (Figure 1B), whereas naproxen and etoricoxib have low similarity (1.04) and clear visual dis-similarity (data not presented). Rofecoxib and etoricoxib have a SHAFTS similarity co-efficient of 1.52 with the notable difference that etoricoxib contains chlorine protruding from the ring based scaffold (Figure 1C).

A.

	Naproxen	Rofecoxib
Naproxen	2	1.01
Etoricoxib	1.04	1.52
Pirprofen	1.56	0.98

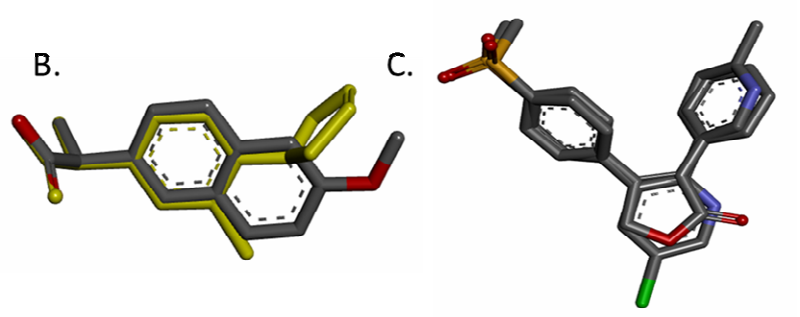

Figure 1A. Table insert showing SHAFTS 3D similarity coefficients of selected NSAIDs; B. Naproxen overlaid with pirprofin; C. Rofecoxib overlaid with etoricoxib.

Conclusion: NSAID classes contain common ring based scaffolds. While 3D similarities exist between "safe" and "non-safe" NSAIDs, subtle structural differences were observed. The out of plane aromatic ring group of prirprofen that forms the main difference between naproxen and

pirprofen may be hypothesised to be mechanistically relevant to the ADR profile of pirprofen. Conversely, the chlorine substituent on etoricoxib's aromatic ring may be providing a steric effect that prevents etoricoxib from interacting with ADR mediating proteins in the same way as rofecoxib, thus creating a different safety profile. This preliminary data highlights differences between safe and unsafe molecules and provides some rationale for considering adverse effect mechanisms. Future work will include attempting to correlate 3D structures with interactions to possible off-targets to inform the design of safer NSAIDs.